



General

Guideline Title

Mitotane for the management of adrenocortical carcinoma.

Bibliographic Source(s)

Alberta Provincial Endocrine Tumour Team. Mitotane for the management of adrenocortical carcinoma. Edmonton (Alberta): CancerControl Alberta; 2013 Nov. 9 p. (Clinical practice guideline; no. ENDO-005). [24 references]

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

1. Patients with resectable adrenocortical carcinoma (ACC). Adjuvant mitotane has been shown to delay or prevent disease recurrence in patients with resected ACC. Adjuvant mitotane should be considered for use in this setting.
 - Mitotane is administered orally, beginning with a dose of 2–6 g per day, in divided doses given q 6 to 8 hours. The dose should then increase by 1 g per day, once every 1 to 2 weeks, to a maximum tolerated dose. The usual dose is 8–10 g per day, in divided doses, but the maximum tolerated dose may vary. The maximum dose should not exceed 19 g per day (British Columbia Cancer Agency, 2013).
 - Patients with potential residual disease (R1 or R_x resection) and/or Ki67 more than 10% should be offered adjuvant mitotane.
2. Patients with advanced unresectable ACC. Mitotane-based combination therapy has been shown to slow disease progression in patients with advanced unresectable ACC. Therefore, mitotane-based combination therapy is recommended for use in this setting.
 - Combination therapy should consist of continuous oral mitotane titrated to a blood level of 14–20 mg/L, followed 1 week later by chemotherapy consistent with the recommendations from the FIRM-ACT study. Doxorubicin (40 mg/m² intravenous [IV] on day 1), etoposide (100 mg/m² IV on days 2, 3, and 4), and cisplatin (40 mg/m² IV on days 3 and 4), given in 4-week cycles or streptozocin (1 g on days 1 to 5 in cycle 1; 2 g on day 1 in subsequent cycles) every 3 weeks are both options that can be considered for patients appropriate for treatment with chemotherapy (Fassnacht et al., 2012).

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Adrenocortical carcinoma (ACC)

Guideline Category

Management

Treatment

Clinical Specialty

Endocrinology

Oncology

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide evidence-based recommendations on the use of mitotane in patients with adrenocortical carcinoma (ACC) and to define which patients are acceptable candidates for treatment with this agent

Target Population

Patients diagnosed with adrenocortical carcinoma (ACC)

Interventions and Practices Considered

1. Adjuvant mitotane therapy following resection for resectable adrenocortical carcinoma (ACC)
2. Mitotane-based combination therapy for advanced unresectable disease

Major Outcomes Considered

- Survival rate (5-year, overall)
- Response rate (overall, complete, partial)
- Recurrence rate
- Time to progression
- Mortality
- Adverse events

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Research Questions

Specific research questions to be addressed by the guideline document were formulated by the guideline lead(s) and Knowledge Management (KM) Specialist using the PICO question format (patient or population, intervention, comparisons, outcomes).

Guideline Questions

- Does adjuvant mitotane delay recurrence or prolong survival in patients with resectable adrenocortical carcinoma? If so, what is the appropriate dosing regimen for mitotane in this setting?
- Does mitotane, in combination with other anti-tumour agents, prolong survival in patients with advanced unresectable adrenocortical carcinoma? If so, which combination is most effective, and at what dose, in this setting?

Search Strategy

The PubMed and Medline databases were searched (1965 through 2013 July 16) for relevant publications using the following search terms: (*mitotane* or *lysodren*) and (*adrenocortical carcinoma* or [*adrenal gland* and *neoplasm*]). Results were limited to randomized controlled trials, phase II-III clinical trials, meta-analyses, and guidelines. In addition, the National Guideline Clearinghouse database was searched (2008 through 2013 July 16) for additional guidelines and the American Society of Clinical Oncology (ASCO) meeting abstracts database was searched (2011 through 2013 July 16) for relevant abstracts. A total of eleven and fifteen citations were returned from PubMed and Medline, respectively; seven were relevant and therefore included in the literature review. One ASCO abstract was included as well. No additional guidelines were identified in the National Guideline Clearinghouse database; however, protocols for the use of mitotane were retrieved from the BC Cancer Agency website.

Number of Source Documents

A total of eleven and fifteen citations were returned from PubMed and Medline, respectively; seven were relevant and therefore included in the literature review. One ASCO abstract was included as well. No additional guidelines were identified in the National Guideline Clearinghouse database; however, protocols for the use of mitotane were retrieved from the BC Cancer Agency website.

Methods Used to Assess the Quality and Strength of the Evidence

Not stated

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Endocrine Tumour Team and a

Knowledge Management (KM) Specialist from the Guideline Utilization Resource Unit (GURU). A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Utilization Resource Unit Handbook](#) (see the "Availability of Companion Documents" field).

Evidence Tables

Evidence tables containing the first author, year of publication, patient group/stage of disease, methodology, and main outcomes of interest are assembled using the studies identified in the literature search. Existing guidelines on the topic are assessed by the KM Specialist using portions of the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument (<http://www.agreetrust.org>) and those meeting the minimum requirements are included in the evidence document. Due to limited resources, GURU does not regularly employ the use of multiple reviewers to rank the level of evidence; rather, the methodology portion of the evidence table contains the pertinent information required for the reader to judge for himself the quality of the studies.

Evidence is summarized in the table in Appendix B in the original guideline document.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Formulating Recommendations

The working group members formulated the guideline recommendations based on the evidence synthesized by the Knowledge Management (KM) Specialist during the planning process, blended with expert clinical interpretation of the evidence. As detailed in the [Guideline Utilization Resource Unit Handbook](#) (see the "Availability of Companion Documents" field), the working group members may decide to adopt the recommendations of another institution without any revisions, adapt the recommendations of another institution or institutions to better reflect local practices, or develop their own set of recommendations by adapting some, but not all, recommendations from different guidelines.

The degree to which a recommendation is based on expert opinion of the working group and/or the Provincial Tumour Team members is explicitly stated in the guideline recommendations. Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations, the Guideline Utilization Resource Unit (GURU) does not use formal rating schemes for describing the strength of the recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This guideline was reviewed and endorsed by the Alberta Provincial Endocrine Tumour Team.

When the draft guideline document has been completed, revised, and reviewed by the Knowledge Management Specialist and the working group members, it is sent to all members of the Provincial Tumour Team for review and comment. This step ensures that those intended to use the

guideline have the opportunity to review the document and identify potential difficulties for implementation before the guideline is finalized. Depending on the size of the document, and the number of people it is sent to for review, a deadline of one to two weeks will usually be given to submit any feedback. Ideally, this review will occur prior to the annual Provincial Tumour Team meeting, and a discussion of the proposed edits will take place at the meeting. The working group members will then make final revisions to the document based on the received feedback, as appropriate. Once the guideline is finalized, it will be officially endorsed by the Provincial Tumour Team Lead and the Executive Director of Provincial Tumour Programs.

Evidence Supporting the Recommendations

References Supporting the Recommendations

British Columbia Cancer Agency (BCCA). Cancer drug manual: mitotane.. [internet]. 2009 (revised 2013 Jun 1) [accessed 2013 Jul 25].

Fassnacht M, Terzolo M, Allolio B, Baudin E, Haak H, Berruti A, Welin S, SchadeBrittinger C, Lacroix A, Jarzab B, Sorbye H, Torpy DJ, Stepan V, Scheingart DE, Arlt W, Kroiss M, Leboulleux S, Sperone P, Sundin A, Hermesen I, Hahner S, Willenberg HS, Tabarin A, Quinkler M, de la Fouchardière C, Schlumberger M, Mantero F, Weismann D, Beuschlein F, Gelderblom H, Wilmink H, Sender M, Edgerly M, Kenn W, Fojo T, MÅller HH, Skogseid B, FIRM-ACT Study Group. Combination chemotherapy in advanced adrenocortical carcinoma. *N Engl J Med*. 2012 Jun 7;366(23):2189-97. [PubMed](#)

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of mitotane for the management of adrenocortical carcinoma (ACC)

Potential Harms

Refer to Appendix B in the original guideline document for adverse events associated with mitotane treatment reported in the literature.

Qualifying Statements

Qualifying Statements

The recommendations contained in this guideline are a consensus of the Alberta Provincial Endocrine Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Implementation of the Guideline

Description of Implementation Strategy

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services Web site.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

End of Life Care

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Alberta Provincial Endocrine Tumour Team. Mitotane for the management of adrenocortical carcinoma. Edmonton (Alberta): CancerControl Alberta; 2013 Nov. 9 p. (Clinical practice guideline; no. ENDO-005). [24 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Nov

Guideline Developer(s)

CancerControl Alberta - State/Local Government Agency [Non-U.S.]

Source(s) of Funding

CancerControl Alberta

Guideline Committee

Alberta Provincial Endocrine Tumour Team

Composition of Group That Authored the Guideline

Members of the Alberta Provincial Endocrine Tumour Team include medical oncologists, endocrinologists, surgeons, and nurses.

Financial Disclosures/Conflicts of Interest

Participation of members of the Alberta Provincial Endocrine Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Endocrine Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the [Alberta Health Services Web site](#) .

Availability of Companion Documents

The following is available:

- Guideline utilization resource unit handbook. Edmonton (Alberta): CancerControl Alberta; 2013 Jan. 5 p. Electronic copies: Available from the [Alberta Health Services Web site](#) .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on August 12, 2014. The information was verified by the guideline developer on September 22, 2014.

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